

> d his

(FILE 'HOME' ENTERED AT 17:20:39 ON 01 NOV 2004)

FILE 'STNGUIDE' ENTERED AT 17:20:47 ON 01 NOV 2004

FILE 'MEDLINE, CAPLUS, BIOSIS, EMBASE, SCISEARCH' ENTERED AT 17:20:58 ON
01 NOV 2004

E MAJEED MUHAMMED/AU

41 S E2-E4

3 S L1 AND BOSWEL?

E BAMAIEV V/AU

E SHAO YU/AU

127 S E3

2 S L3 AND BOSWEL?

E HUANG MOU/AU

209 S E5-E6

4 S L5 AND BOSWEL?

2 DUP REM L6 (2 DUPLICATES REMOVED)

81 S BOSWEL?(L) (AUTO(W)IMMUN? OR PSORIASIS OR SARCOIDOSIS OR ERYTH

50 DUP REM L8 (31 DUPLICATES REMOVED)

15 S L9 NOT PY>=2000

on STN
ACCESSION NUMBER: 1999206199 EMBASE
TITLE: [Salai Guggal - Indian incense for therapy of rheumatoid
arthritis].
SALAI GUGGAL - INDISCHER WEIHRAUCH ZUR BEHANDLUNG DER
RHEUMATOIDEN ARTHRITIS.
AUTHOR: Trubestein G.
CORPORATE SOURCE: Dr. G. Trubestein, An der Heppenmauer 10, D-63619 Bad Orb,
Germany
SOURCE: Biologische Medizin, (1999) 28/3 (121-124).
Refs: 21
ISSN: 0340-8671 CODEN: BIMEFA
COUNTRY: Germany
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 029 Clinical Biochemistry
031 Arthritis and Rheumatism
037 Drug Literature Index
LANGUAGE: German
SUMMARY LANGUAGE: English; German

B Salai Guggal, the gum resin of **Boswellia serrata**, has been used since a long time as a traditional remedy in Ayurveda medicine in India for inflammatory diseases such as rheumatoid **arthritis**, ulcerative colitis and **Crohn's** disease. Compounds from the gum with genuine antiinflammatory effect are the **boswellic** acids. **Boswellic** acids inhibit the leukotriene biosynthesis. The effect is triggered by **boswellic** acids binding the enzyme. In clinical studies in Europe with Salai Guggal promising results were found in patients with rheumatoid **arthritis**. Besides the preparations from India and Switzerland with 400 mg dry extract products of Olibanum are used as Olibanum guttae and Olibanum RA ointment and other homoeopathic preparation.

ANSWER 12 OF 50 CAPLUS COPYRIGHT 2004 ACS on STN
 CESSION NUMBER: 2002:658137 CAPLUS
 CUMENT NUMBER: 137:190761
 TLE: Water soluble boswellic acids, their preparation and
 use for treating inflammatory conditions
 VENTOR(S): Majeed, Muhammed; Badmaev, Vladimir
 TENT ASSIGNEE(S): Sabinsa Corporation, USA
 URCE: PCT Int. Appl., 29 pp.
 CODEN: PIXXD2
 CUMENT TYPE: Patent
 NGUAGE: English
 MILY ACC. NUM. COUNT: 1
 TENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002066491	A1	20020829	WO 2002-US3384	20020215
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				

PRIORITY APPLN. INFO.: US 2001-268713P P 20010215
 A new composition, which can be formed through a method comprising: (a) dissolving mixts. of **boswellic** acids in a water and alc. solution to form a mixture; (b) adding one or more alkali salts to the mixture to form a salt solution; (c) filtering the solution to sep. un-reacted alkali salt from a filtrate; and (d) recovering the soluble **boswellic** acid mixture from the filtrate, is described. Addnl., the new composition can be formed by using super critical carbon dioxide. The new composition can be used to alleviate numerous inflammatory conditions, including, but not limited to, rheumatoid **arthritis** and osteoarthritis, colon cancer, prostate cancer and breast cancer, and a broad range of neurodegenerative conditions, such as Alzheimer's disease and Parkinson's disease. The composition can be administered parenterally, orally, or topically.

10/076,667
abandoned

577124

STIC-ILL

From: Jiang, Shaojia
Sent: Monday, November 01, 2004 6:11 PM
To: STIC-ILL
Cc: Jiang, Shaojia
Subject: please pull out these 09/926424

NPL _____ Adonis _____
MIC _____ Tech _____
NO. X NO. _____ NOS _____
Ck Cite _____ Dupl Request _____
Call # 110

L9 ANSWER 38 OF 50 CAPLUS COPYRIGHT 2004 ACS on STN DUPLICATE 7
ACCESSION NUMBER: 1996:491734 CAPLUS
DOCUMENT NUMBER: 125:185262
TITLE: Anti-inflammatory actions of boswellic acids
AUTHOR(S): Singh, G. B.; Singh, Surjeet; Bani, Sarang
CORPORATE SOURCE: Regional Research Laboratory, Department
Pharmacology,
Jammu Tawi, 180 001, India
SOURCE: Phytomedicine (1996), 3(1), 81-85
CODEN: PYTOEY; ISSN: 0944-7113
PUBLISHER: Fischer
DOCUMENT TYPE: Journal
LANGUAGE: English

15463772

ACCESSION NUMBER: 1999206199 EMBASE
TITLE: [Salai Guggal - Indian incense for therapy of rheumatoid
arthritis].
SALAI GUGGAL - INDISCHER WEIHRAUCH ZUR BEHANDLUNG DER
RHEUMATOIDEN ARTHRITIS.
AUTHOR: Trubestein G.
CORPORATE SOURCE: Dr. G. Trubestein, An der Heppenmauer 10, D-63619 Bad
Orb,
Germany
SOURCE: Biologische Medizin, (1999) 28/3 (121-124).
Refs: 21
ISSN: 0340-8671 CODEN: BIMEFA
COUNTRY: Germany
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 029 Clinical Biochemistry
031 Arthritis and Rheumatism
037 Drug Literature Index
LANGUAGE: German
SUMMARY LANGUAGE: English; German

ACCESSION NUMBER: 2001:447633 CAPLUS
DOCUMENT NUMBER: 135:220902
TITLE: Anti-tumor and anti-carcinogenic activities of
triterpenoid, .beta.-boswellic acid
AUTHOR(S): Huang, Mou-Tuan; Badmaev, Vladimir; Ding,
Yu; Liu, Yue; Xie, Jian-Guo; Ho, Chi-Tang
CORPORATE SOURCE: Laboratory for Cancer Research, College of Pharmacy,

Gustav Trübestein

Salai Guggal – Indischer Weihrauch zur Behandlung der rheumatoiden Arthritis

Zusammenfassung

Salai Guggal, das Harz des indischen Weihrauchbaums, wird in Indien in der traditionellen Medizin (Ayurveda) seit langem zur Behandlung von entzündlichen Erkrankungen wie der rheumatoiden Arthritis, Colitis ulcerosa und Morbus Crohn eingesetzt. Inhaltsstoffe des Weihrauchs, die an der entzündungshemmenden Wirkung beteiligt sein dürften, sind Boswelliasäuren; diese führen zu einer Hemmung der Leukotrien-Biosynthese. Die Wirkung erfolgt nach Bindung von Boswelliasäuren an das Enzym.

Klinische Untersuchungen in Europa mit dem Harz des indischen Weihrauchbaums erwiesen sich als wirksam bei der rheumatoiden Arthritis. Neben den handelsüblichen Präparaten aus Indien und der Schweiz mit 400 mg Trockenextrakt werden Weihrauchprodukte auch als Olibanum RA Tropfen und Olibanum RA Salbe und anderen homöopathischen Zubereitungen gegeben.

Schlüsselwörter: Boswelliasäuren, chronische rheumatoide Arthritis, Leukotriene, Weihrauch

Einleitung

Die Verwendung von Weihrauch (Olibanum) ist eng mit der kulturgeschichtlichen Nutzung von Geruchsstoffen und Räucherwerk für kultische und hygienische Zwecke verbunden. Im klassischen Altertum unseres Kulturkreises nahm die Bedeutung der natürlichen Harze des Weihrauchbaumes (Olibanum) aus dem arabischen Raum stark zu.

Das primäre Verbreitungsgebiet des Weihrauchbaumes umfaßt im wesentlichen Somalia, Nubien, Südarabien, Äthiopien und Teile des tropischen Afrika (Olibanum) sowie insbesondere Indien (Salai Guggal).

Das Harz des indischen Weihrauchbaums (Salai Guggal) wird in der traditionellen indischen Medizin (Ayurveda) seit Jahrtausenden eingesetzt, insbesondere bei entzündlichen Erkrankungen wie rheumatoider Arthritis und Osteoarthritis sowie auch bei zervikaler Spondylosis deformans. Die Applikation erfolgt in Form von Salben, Extrakten und Pulvern (5, 12, 13, 14). Im wesentlichen handelt es sich hierbei um das Gummiharz von *Boswellia serrata* Roxb. Die Menge, die jährlich von einem Baum in Indien gewonnen werden kann, wird auf zirka 1 kg geschätzt (12, 13). Die jährliche Ernte an indischem Weihrauch liegt über 1 000 Tonnen.

Hauptbestandteile dieses Gummiharzes sind neben *Boswellia serrata* Roxb. ätherische Öle, Terpinole, Arabinose, Xylose, Galaktose, Galakturonsäuren, Beta-Sitosterin und Phlobaphene.

Eine exakte Zuordnung der handelsüblichen Weihrauchsorten zu ihrer botanischen Herkunft ist oft nicht möglich, zu-

mal der Weihrauch häufig in gemischter Form auf den Markt gelangt. Eine nachvollziehbare Qualitätskontrolle für die medizinische Anwendung ist unter diesen Umständen äußerst schwierig, obwohl sie notwendig wäre. Darüber hinaus sind die Harze des Weihrauchs (Olibanum) und des indischen Weihrauchs (Salai Guggal) klassische pflanzliche Vielstoffgemische mit den entsprechenden Eigenheiten in Qualitätssicherung, Forschung und Anwendung (17). Bislang sind jeweils mehr als 200 Inhaltsstoffe im Harz des Weihrauchs (Olibanum) identifiziert worden (13, 14, 19). Es ist anzunehmen, daß die Verhältnisse bei dem indischen Weihrauch vergleichbar komplex sind.

Wirkungsmechanismus

Indischer Weihrauch hemmt nach den vorliegenden Untersuchungen konzentrationsabhängig die Synthese von Leukotrienen (11). Die Ergebnisse von Ammon legen die Vermutung nahe, daß die azetylierten Boswelliasäuren des Weihrauchbaumes in der Arachidonsäurekaskade die Bildung von Leukotrienen hemmen (1, 2). Ein antioxidativer Effekt – wie bei anderen bekannten Hemmstoffen der Leukotrienbiosynthese – konnte nicht gefunden werden (3).

Über die Hemmwirkung auf die Leukotrienbiosynthese hinaus wurde in der Zwischenzeit auch berichtet, daß Boswelliasäuren, allerdings in wesentlich höheren Konzentrationen, in vitro auch die Proliferation von Tumorzellen wie HL 60 und CCRF-CEM (7) Glioblastomzellen (4) und Melanomzellen (3) hemmen.

Leukotriene verfügen über eine Reihe von Wirkungen, von denen die meisten am Entzündungsgeschehen beteiligt sind.

Möglicherweise könnte eine Hemmung der Komplementaktivierung zu der antiinflammatorischen Wirkung beitragen (8, 10, 20).

Forschungsergebnisse

Experimentelle Forschung

In der experimentellen Forschung wurden

Summary

Salai Guggal, the gum resin of *Boswellia serrata*, has been used since a long time as a traditional remedy in Ayurveda medicine in India for inflammatory diseases such as rheumatoid arthritis, ulcerative colitis and Crohn's disease. Compounds from the gum with genuine anti-inflammatory effect are the boswellic acids. Boswellic acids inhibit the leukotriene biosynthesis. The effect is triggered by boswellic acids binding the enzyme.

In clinical studies in Europe with Salai Guggal promising results were found in patients with rheumatoid arthritis. Besides the preparations from India and Switzerland with 400 mg dry extract products of *Olibanum* are used as *Olibanum guttae* and *Olibanum RA ointment* and other homoeopathic preparation.

Keywords: *Boswellia* resin, boswellic acids, leukotrienes, rheumatoid arthritis

unterschiedliche Fraktionen aus dem Gummiharz des Weihrauchbaumes verwendet, die jedoch im wesentlichen Boswelliasäuren enthielten (14, 15). Die experimentellen Untersuchungen mit dem Rohharz und seinen verschiedenen Extrakten und Fraktionen wie auch mit Boswelliasäuren weisen auf deutliche, dosisabhängige antiinflammatorische Wirkungen hin (3, 6, 16).

Klinische Forschung

In der klinischen Forschung wurden vor allem die in Indien und in der Schweiz erhältlichen Präparate aus Salai Guggal in Tablettenform eingesetzt. Dementsprechend unterscheiden sich die experimentell und klinisch untersuchten Zubereitungen; dies erschwert die pharmakologische Beurteilung. Die hier angesprochenen Zubereitungen enthalten jedoch alle ein ausreichendes Gemisch aus Boswelliasäuren, so daß die experimentell mit Extrakten ermittelten Ergebnisse mit den klinischen vergleichbar sind.

Klinische Untersuchungen

Zur Beurteilung der therapeutischen Anwendungen mit Salai-Guggal-Gummiharz – im wesentlichen *Boswellia serrata* – liegen neben einzelnen Berichten und Beobachtungsserien einige kleinere, zumeist offene Studien vor. Zum Einsatz kamen Präparate aus Indien wie Sallaki-Tabletten, gewonnen aus dem Rohharz mit 200 mg oder 400 mg Trockenextrakt. Sie entsprechen den über einen Schweizer Kanton vertriebenen H15 Ayurvedica-Tabletten, die 400 mg Trockenextrakt *Boswellia serrata* enthalten.

Die Präparate wurden bei Patienten mit rheumatoider Arthritis, Patienten mit Colitis ulcerosa und Morbus Crohn sowie auch bei Patienten mit Hirntumoren, insbesondere bei tumor- und operationsbedingtem Ödem eingesetzt. Für die Beurteilung der Erfahrungen mit Salai Guggal aus Indien müssen allerdings auch Gesichtspunkte der traditionellen Krankheitslehre und Arzneimittelcharakterisierung (Ayurvedische Regulationslehre) mit berücksichtigt werden, um Fehlinterpretationen der Ergebnisse zu vermeiden (21).

Inhaltsstoffe	Prozent
Wasser	10–12
Harz	55–57
Gummi	20–23
ätherisches Öl	8–9
unlösliche Bestandteile	4–5

Tab.: Hauptinhaltsstoffe des Weihrauchs aus *Boswellia serrata* (aus: Kluge H, Fernando RC, Weihrauch und seine heilende Wirkung. Heidelberg: Karl F. Haug 1998)

Ergebnisse der klinischen Untersuchungen

Im Vordergrund der klinischen Untersuchungen standen in der Schweiz und Deutschland der Einsatz von Salai-Guggal-Gummiharz aus *Boswellia serrata* bei Patienten mit rheumatoider Arthritis. Die Ergebnisse kontrollierter Studien fielen unterschiedlich aus. 1994 wurden auf der Tagung der Deutschen Gesellschaft für Rheumatologie zwei plazebokontrollierte Doppelblindstudien bei Patienten mit langjähriger rheumatoider Arthritis vorgestellt, die unter einer Basistherapie unverändert entzündliche Aktivitäten aufwiesen. Über 12 Wochen wurde H15 Ayurvedica (ebi pharm, Kirchliedach/Schweiz) oder Plazebo gegeben (in der 1. Woche 1 200 mg/Tag, in den nachfolgenden 11 Wochen je nach Gruppenzuteilung 2 400 mg beziehungsweise 3 600 mg/Tag H15 Ayurvedica). Die Auswertung der Daten von 81 Patienten ergab, daß Gelenkschwellungen, Gelenkschmerzhaftigkeit, Morgensteifigkeit, Schmerzintensität und als laborchemischer Parameter die Blutkörperchensenkungsgeschwindigkeit (BSG) in der H15-Ayurvedica-Gruppe im Vergleich zu der Plazebogruppe vermindert waren. Auch war die Abbruchrate unter der H15-Ayurvedica-Medikation geringer als unter Plazebo (9). Eine 1998 publizierte Teilauswertung eines Zentrums mit 37 Patienten der multizentrischen Studie zeigte jedoch keine signifikanten oder klinisch bedeutsamen Unterschiede zwischen der H15-Ayurvedica-Gruppe und der Plazebogruppe bei den gewählten klinischen und serologischen Parametern (18).

Es kann somit festgehalten werden, daß

für H15 Ayurvedica (Trockenextrakt aus *Boswellia serrata* des indischen Weihrauchs) bei der rheumatoiden Arthritis erste, weitgehend noch unpublizierte Erfahrungen und kleinere Studien vorliegen.

Wertung der Ergebnisse

Bei der rheumatoiden Arthritis handelt es sich um ein von der Intensität der Beschwerden her stark wechselhaftes Krankheitsbild. Zur Behandlung der akuten Schmerzsymptomatik im Rahmen eines neuen Krankheitsschubs und zur Behandlung neu aufgetretener schmerzhafter Bewegungseinschränkungen ist der indische Weihrauch nach den bisher vorliegenden Untersuchungen nicht geeignet. Bei einem akuten Schub der rheumatoiden Arthritis haben nichtsteroidale Antirheumatika, Kortikosteroide und physiotherapeutische Maßnahmen die Priorität. Obwohl große und ausreichend lang durchgeführte kontrollierte Untersuchungen mit Salai-Guggal-Gummiharz aus *Boswellia serrata* noch fehlen, kann für die Langzeittherapie der rheumatoiden Arthritis diese Medikation in Betracht gezogen werden, da die Ergebnisse bei dieser Indikation vielversprechend sind.

Nebenwirkungen

Das Harz aus *Boswellia*-arten hat eine äußerst geringe Toxizität, Nebenwirkungen werden bei bestimmungsgemäßem Gebrauch nur in geringem Umfang beobachtet. Selten treten bei mit H15 Ayurvedica behandelten Patienten mit chronischer Polyarthritis und Spondylarthritis ankylopoetica gastrointestinale Beschwerden auf – auch nach eigenen Beobachtungen. Allergische Reaktionen sind nur vereinzelt beobachtet worden.

Verbreitung

Unter dem indischen Handelsnamen Salalai werden Tabletten aus dem Rohharz angeboten, die 200 mg beziehungsweise 400 mg Trockenextrakt enthalten. Sie entsprechen den über einen Schweizer Kanton vertriebenen H15 Ayurvedica-Tabletten (*Boswellia serrata*). Das frühere Bundesgesundheitsamt (heute Bundesinstitut für Arzneimittel und Medizinprodukte) in Berlin hat vor einigen Jahren einen Antrag

auf Zulassung des Weihrauchpräparates H15 in Deutschland für die Indikation rheumatoide Arthritis mangels hinreichender wissenschaftlicher Unterlagen abgelehnt.

Indikationen

Entsprechend den klinischen Erfahrungen, die zu einer Registrierung von H15 Ayurvedica im Halbkanton Appenzell / Außerrhoden der Schweiz führten, wird Salai-Guggal-Gummiharz aus *Boswellia serrata* bei rheumatoider Arthritis eingesetzt. Dabei ist festzuhalten, daß es sich bei der rheumatoiden Arthritis um ein von der Intensität der Beschwerden her stark wechselhaftes Krankheitsbild handelt. Zur Behandlung der akuten Symptome im Rahmen eines erneuten Krankheitsschubs und zur Behandlung neu aufgetretener Beschwerden ist der indische Weihrauch, auch nach den Herstellerangaben, nicht geeignet. H15 Ayurvedica kann jedoch für die Langzeittherapie der rheumatoiden Arthritis eingesetzt werden, zumal die Nebenwirkungsrate sehr gering ist. Weitere Indikationen für den indischen Weihrauch (Salai-Guggal-Gummiharz) wie Colitis ulcerosa und Morbus Crohn befinden sich in Abklärung.

Neben diesen Präparaten werden Weihrauchprodukte auch als homöopathische Urtinktur (z.B. Olibanum RA-Tropfen) und andere homöopathische Zubereitungen im Niederpotenzbereich ohne Angaben einer therapeutischen Indikation angeboten. Darüber hinaus wird Weihrauch auch als Nahrungsergänzungsmittel (z.B. Vita Weihrauchkapseln) vertrieben.

Vorgehen in der Praxis

Da der indische Weihrauch als Therapieprinzip durch die Laienpresse den Patienten bekannt geworden ist, wird der behandelnde Arzt von Patienten mit rheumatoider Arthritis häufiger auf diese Medikation angesprochen. So hat H15 Ayurvedica nicht nur in der Schweiz sondern auch in Deutschland eine größere Verbreitung gefunden, wobei in der Regel Tabletten zu 400 mg (Trockensubstanz) verordnet werden. Salai-Guggal-Gummiharz aus *Boswellia serrata* wird als Arzneimittel entwe-

der aus Indien oder unter der Bezeichnung H15 Ayurvedica (*Boswellia serrata*) aus der Schweiz bezogen. Die Kosten für 100 Tabletten H15 Ayurvedica à 400 mg betragen zur Zeit bei Bezug aus der Schweiz ca. DM 100,- (unverbindliche Preisempfehlung des Importeurs). Als Dosierung werden zu Beginn der Therapie täglich 3mal 2 Tabletten à 400 mg, später 3mal 1 Tablette à 400 mg empfohlen. Nach den bisherigen Erfahrungen setzt die Wirkung des Weihrauchpräparates langsam ein, meist erst nach 4–6 Wochen. Eine Begleitmedikation zur Verminderung der Schmerzen des Patienten wird deshalb zu Beginn der Behandlung mit H15 Ayurvedica erforderlich sein.

Literatur

- 1 Ammon HPT. Salai Guggal – *Boswellia serrata*: from a herbal medicine to a specific inhibitor of leukotrien biosynthesis. *Phytomedicine* 1996;3:67–70
- 2 Ammon HPT. *Boswellia*-Säuren. Hemmstoffe der Leukotrien-Biosynthese. *Dr Apoth Ztg* 1997;137:53–4
- 3 Ammon HPT. Salai-guggal-(Indischer Weihrauch)Gummiharz aus *Boswellia serrata*. *Dr Ärztebl* 1998;95:8 24–5
- 4 Böker K, Winking M. Die Rolle von *Boswellia*-Säuren in der Therapie maligner Gliome. *Dr Ärztebl* 1997;94A 1197–9
- 5 DAZ Interview. Weihrauch – ein neuer Weg in der Therapie von Entzündungen? Interview mit Prof. Dr. Ammon. *Dr Apoth Ztg* 1992;132:2442–4
- 6 Etzel R. Special extract of *Boswellia serrata* (H15) in the treatment of rheumatoid arthritis. *Phytomedicine* 1996;3:91–4
- 7 Hoernlein RF, Orlikowsky F, Zehrer C, Niethammer D, et al. Acetyl-11-keto-boswellic acid induces apoptosis in HL60 and CCRF-CEM cells and inhibits topoisomerase I. *Proc Am Assoc Canc Res* 1997;7:1291
- 8 Kapil A, Moza N. Anti-complementary activity of boswellic acids – an inhibitor of C3-convertase of the classical complement pathway. *Int J Immunopharmacol* 1992;14:1139–43
- 9 Keudell C von, et al. Klinische Wirksamkeit des Weihrauchpräparates H15 bei rheumatoider Arthritis: Ein neues Therapieprinzip durch spezifische 5-Lipoxygenasen-Inhibition? *Rheumatol* 1994;53(Suppl.1):144
- 10 Knaus U, Wagner H. Effects of boswellic acid of *Boswellia serrata* and other triterpenic acids on the complement system. *Phytomedicine* 1996;3:77–81
- 11 Kroegel E, et al. 5-Lipoxygenase-Inhibitoren und Leukotrien-Rezeptorantagonisten. Pathophysiologische Grundlagen und klinische Anwendung. *Arzneimitteltherapie* 1996;14:299–309
- 12 Martinetz D. Der indische Weihrauch – neue Aspekte eines alten Harzes. *Phytotherapie* 1992;13:121–5
- 13 Martinetz D, Lohs K, Janzen J. Weihrauch und Myrrhe. Kulturgeschichte und wirtschaftliche Bedeutung. Botanik, Chemie, Medizin. Stuttgart: Wissenschaftliche Verlagsgesellschaft 1989
- 14 Sabieraj J. *Boswellia*. In: Hager E (Hrsg.). Hagers Handbuch der Pharmazeutischen Praxis, Folgeband 2 (Drogen A–K). 5. Auflage. Berlin: Springer 1998;245–52

- 15 Safayhi H, Ammon HPT. Pharmakologische Aspekte von Weihrauch und Boswelliasäuren. *Pharm Ztg* 1997;142: 3277-86
- 16 Safayhi H, Sailer ER. Anti-inflammatory actions of pentacyclic triterpenes. *Planta Med* 1997;63:487-93
- 17 Saller R, Reichling J, Hellenbrecht D. Phytotherapie. Klinische, pharmakologische und pharmazeutische Grundlagen. Heidelberg: Karl F. Haug 1995
- 18 Sander O, et al. Ist H15 (Harzextrakt von *Boswellia serrata*, „Weihrauch“) eine sinnvolle Ergänzung zur eta-

- blierten Therapie der chronischen Polyarthritis? — Ergebnisse einer doppelblinden Pilotstudie. *Z Rheumatol* 1998;57:11-6
- 19 Sellar W. Weihrauch und Myrrhe. Anwendung in Geschichte und Gegenwart. München: Droemersch Verlagsanstalt 1997
- 20 Wagner H, Knaus W, Jordan E. Pflanzeninhaltsstoffe mit Wirkung auf das Komplementsystem. *Z Phytother* 1987;8:148-9
- 21 Zoller A, Nordwig H. Heilpflanzen der Ayurvedischen Me-

dizin. Ein praktisches Handbuch. Heidelberg: Karl F. Haug 1997

Anschrift des Verfassers

Prof. Dr. med. Gustav Trübestein
An der Heppenmauer 10
D-63619 Bad Orb



AKTUELLER BERICHT

HOT – Hypertension Optimal Treatment:

Größte abgeschlossene Hochdruck-Interventionsstudie

Die HOT-Studie wurde durchgeführt, um definitive Aussagen für eine optimierte Hochdruck-Therapie zu erhalten. Der Schlaganfall und die koronare Herzkrankheit sind die schwerwiegendsten Komplikationen der arteriellen Hypertonie. Die Empfehlungen nationaler und internationaler Gremien (Deutsche Hochdruck-Liga, JNC [Joint National Committee of Prevention] und WHO / ISH) haben als Zielkriterium einen diastolischen Blutdruck von unter 90 mmHg als erstrebenswert definiert, wobei der systolische Blutdruck auf Werte unter 140 mmHg gesenkt werden sollte.

Eine Metaanalyse von 14 Interventionsstudien aus dem Jahr 1990 an ca. 37 000 Patienten mit essentieller Hypertonie zeigte, daß das Schlaganfallrisiko unter einer antihypertensiven Therapie um ca. 40% abnimmt. Bei koronaren Ereignissen fand sich jedoch nur eine Reduktion um 12%. Mögliche Ursachen für die geringe Beeinflussung der koronaren Herzkrankheit durch eine antihypertensive Therapie sind offenbar die nicht ausreichende Behandlung weiterer Risikofaktoren; darüber hinaus war bisher nicht geklärt, ob der anzustrebende diastolische Blutdruck mit 90 mmHg diastolisch nicht zu hoch angesetzt war.

Um die Therapiesicherheit zu erhöhen, wurde die HOT-Studie nach dem Probe-Design (prospektiv, randomisiert, offen, mit verblindeter Bewertung der Zielkriterien) durchgeführt; nunmehr beendet ist sie die zur Zeit größte, abgeschlossene Hochdruck-Interventionsstudie.

Die HOT-Studie hatte folgende Zielparameter:

- Ausmaß der Reduktion in der kardio-

vaskulären Morbidität und Mortalität unter der antihypertensiven Therapie bei Patienten mit den angestrebten drei diastolischen Blutdruckwerten von ≤ 90 mmHg, ≤ 85 mmHg und ≤ 80 mmHg.

- Zusammenhang zwischen den erreichten Blutdruckwerten und dem Risiko der kardiovaskulären Morbidität und Mortalität.
- Senkung des Risikos von kardiovaskulärer Morbidität und Mortalität bei zusätzlicher Gabe von 75 mg ASS/Tag, verglichen mit Placebo.

Methode

18 790 Patienten aus 26 Ländern mit einem Alter von 50-80 Jahren (im Mittel: 61,5 Jahre) mit einer Hypertonie und diastolischen Blutdruckwerten zwischen 100-115 mmHg (im Mittel: 105 mmHg) wurden in drei Gruppen mit anzustrebenden diastolischen Werten ≤ 90 mmHg, ≤ 85 mmHg und ≤ 80 mmHg randomisiert. Entsprechend diesen Zielparametern wurden folgende Gruppen gebildet:

bei 6 264 Patienten war der Ziel-Blutdruck ≤ 90 mmHg;

bei 6
 ≤ 85
bei 6
 ≤ 80

Die
Felod
Astra
tionse

Um m
senku
Blutd
messu
Subst
xis ge
zu H
vergli
lierten
schied
Studie
de gel

Die H
heit d
druck
antago
in Kor
oder E
beibeh
Patient
druck
Basist
schnitt
der HO
verglei
dipin 5
gut ve
chen E
nahme
Hochd
Basisth

Die H
deutlic
Blutdr
schwer
duziert
ten auc
wichtig
einer k
folgend

STIC-ILL

577/22

From: Jiang, Shaojia
Sent: Monday, November 01, 2004 6:11 PM
To: STIC-ILL 1617
Cc: Jiang, Shaojia
Subject: please pull out these 09/926424

NPL _____ Adonis _____
MIC _____ BioTech _____ MAIN _____
NO 6 Vol NO _____ NOS _____
Ck Cite 11/2 Dupl Request WIC
Call # _____

L9 ANSWER 38 OF 50 CAPLUS COPYRIGHT 2004 ACS on STN DUPLICATE 7
ACCESSION NUMBER: 1996:491734 CAPLUS
DOCUMENT NUMBER: 125:185262
TITLE: Anti-inflammatory actions of boswellic acids
AUTHOR(S): Singh, G. B.; Singh, Surjeet; Bani, Sarang
CORPORATE SOURCE: Regional Research Laboratory, Department
Pharmacology,
Jammu Tawi, 180 001, India
SOURCE: Phytomedicine (1996), 3(1), 81-85
CODEN: PYTOEY; ISSN: 0944-7113
PUBLISHER: Fischer
DOCUMENT TYPE: Journal
LANGUAGE: English

15463743

ACCESSION NUMBER: 1999206199 EMBASE
TITLE: [Salai Guggal - Indian incense for therapy of rheumatoid
arthritis].
SALAI GUGGAL - INDISCHER WEIHRAUCH ZUR BEHANDLUNG DER
RHEUMATOIDEN ARTHRITIS.
AUTHOR: Trubestein G.
CORPORATE SOURCE: Dr. G. Trubestein, An der Heppenmauer 10, D-63619 Bad
Orb,
Germany
SOURCE: Biologische Medizin, (1999) 28/3 (121-124).
Refs: 21
ISSN: 0340-8671 CODEN: BIMEFA
COUNTRY: Germany
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 029 Clinical Biochemistry
031 Arthritis and Rheumatism
037 Drug Literature Index
LANGUAGE: German
SUMMARY LANGUAGE: English; German

ACCESSION NUMBER: 2001:447633 CAPLUS
DOCUMENT NUMBER: 135:220902
TITLE: Anti-tumor and anti-carcinogenic activities of
triterpenoid, .beta.-boswellic acid
AUTHOR(S): Huang, Mou-Tuan; Badmaev, Vladimir; Ding,
Yu; Liu, Yue; Xie, Jian-Guo; Ho, Chi-Tang
CORPORATE SOURCE: Laboratory for Cancer Research, College of Pharmacy,

Anti-inflammatory actions of boswellic acids

G. B. SINGH, SURJEET SINGH and SARANG BANI

Department of Pharmacology, Regional Research Laboratory, Canal Road, Jammu-Tawi 180 001, India.

Summary

Boswellic acids (BA) demonstrated dose-related anti-inflammatory activity (AIA) in acute tests of carrageenan-, histamine- and dextran-induced edema in rats and mice. It elicited inhibitory action on vascular permeability in mice induced by acetic acid. Marked AIA was observed in chronic models of adjuvant-induced polyarthritis and formaldehyde arthritis in rats and bovine serum albumin-induced arthritis in rabbits. It produced significant protective effects in sodium urate gouty arthritis in dogs. BA reduced exudate volume and inhibited leucocyte migration in carrageenan-induced pleurisy in rats. It did not affect the parturition period in pregnant rats or castor oil-induced diarrhea in rats. It failed to exhibit any analgesic or ulcerogenic effects. BA elicited antipyretic activity in rats and rabbits. LD₅₀ of BA was found to be greater than 2 g/kg in rats and mice when administered orally or intraperitoneally.

Key words: boswellic acid, anti-inflammatory activity in rats and mice, carrageenan-, histamine- and dextran induced edema tests, chronic arthritis models.

Introduction

Inflammation and various inflammatory disorders including rheumatoid arthritis are prevalent all over the world. They afflict large percentage of the world's population and are usually treated with chemical compounds that either inhibit synthesis of prostaglandins (PGs) *e.g.* salicylates or the formation of PGs and leukotrienes, *e.g.*, glucocorticoids. Both PGs and leukotrienes are important mediators of various inflammatory diseases and play vital roles in the development of rheumatoid arthritis and associated disorders. Among the currently available anti-inflammatory drugs, glucocorticoids are much more powerful than those compounds that act only by inhibiting prostaglandin synthesis.

It is well known that since rheumatoid arthritis is a chronic inflammatory disease it needs to be treated with anti-inflammatory drugs over a long period. But these drugs, glucocorticoids specially, produce severe adverse side effects limiting their prolonged use. Consequently, there is a need to develop anti-inflammatory agents that inhibit the synthesis of either leukotrienes alone or leukotrienes and PGs together without producing adverse effects.

Over the past decade we have been actively engaged in

the research and development of new anti-inflammatory agents based on natural sources (Singh et al., 1984; 1986; 1987; 1992; 1993; 1994; Singh and Singh, 1994) that selectively inhibit without adverse effects the synthesis of leukotrienes alone (Ammon et al., 1991) or leukotrienes and PGs. As a result of this investigation an alcoholic extract of gum resin exudate of *Boswellia serrata*, which has been marketed in India under the brand name of Sallaki since 1982 with no reported side effects (Singh and Atal, 1986). This product based on our technology is also being marketed under the brand name H-15 in Switzerland. β -boswellic acid and their derivatives have been isolated as its active constituents and have been found to exert a selective inhibitory action on the formation of 5-lipoxygenase product leukotriene formation (Safayhi et al., 1992).

Materials and Methods

Materials: The boswellic acids (BA) fraction is a partially purified material of triterpene acids obtained from gum resin of the *Boswellia serrata*. The BA fraction is prepared by extracting *Boswellia serrata* gum resin with methanol (95%), removing the non-acidic constituents and precipi-

tating the acids then drying them into a fine powder (Singh et al., 1993).

Methods: Experiments were performed on male Charles Foster rats (110–150 g), Swiss albino mice (22–28 g) and Himalayan strain rabbits (1.5–2.5 kg) maintained at a room temperature of $25 \pm 1^\circ\text{C}$. Test drugs were freshly prepared in gum acacia (2% w/v) administered orally 1 h prior to induction of edema in acute tests and once daily in chronic tests. The paw volume of rats was measured with a volume differential meter model 7101 Ugo Basile (Italy). Data were analyzed statistically using Student's T test.

Carrageenan-induced edema in rats

Edema was induced in rats organized into groups of five by injecting 0.1 ml of carrageenan (1% w/v) solution in normal saline (0.9% NaCl w/v) beneath the plantar surface of the left hind paw (Winter et al., 1962). The paw volume was measured immediately and 4 h after the carrageenan injection.

Carrageenan-induced edema in adrenalectomised rats

Adrenalectomy was performed in rats ($n=5$) under anaesthesia. Experiments were done after two days by injecting carrageenan as described above.

Histamine-induced edema in rats

0.1 ml of histamine (0.1% w/v) solution was injected into the hind limb of rats (Horakova and Muratova, 1964).

Dextran-induced edema in rats

0.1 ml of dextran (6% w/v) solution was injected into the subplantar region of the hind paw after 1 h after treatment with the drug (Winter, 1964).

Carrageenan-induced edema in mice

Edema was induced in the left hind limb of the mice ($n=5$) by injecting 0.05 ml of 1% carrageenan solution by the method described by Singh et al. (1986).

Acetic acid induced vascular permeability in mice

Evan's blue (0.2 ml of 0.25% w/v) solution was injected *i.v.* into mice ($n=5$) 30 min following oral drug treatment (Whittle, 1964). After 15 min, 1 ml/100 g of acetic acid (0.6% v/v) solution was *i.p.* injected, the peritoneal cavity was washed with 5 ml of heparinised saline and the dye content was measured spectrophotometrically.

Cotton pellet-induced granuloma in rats

Autoclaved cotton pellets (50 ± 1 mg) were implanted under each axilla and groin region under ether anaesthesia (Winter and Porter, 1957).

Formaldehyde arthritis in rats

Edema was induced by injecting 0.1 ml of formaldehyde (2% v/v) solution into the left hind paw in groups of 5 rats (Selye, 1949).

Adjuvant-induced developing arthritis in rats

Arthritis was induced by injecting 0.05 ml of 0.5% w/v suspension of killed *Mycobacterium tuberculosis* (Difco) finely homogenised in liquid paraffin into the left hind foot (Newbould, 1963). Paw volume was measured and the percent inhibition was calculated on day 14.

Adjuvant-induced established arthritis in rats

Arthritis was induced in rats as described above. Drug treatment was started on day 14 and terminated on day 28 (Newbould, 1969).

Bovine serum albumin (BSA)-induced arthritis in rabbits

Arthritis was produced in rabbits ($n=4$) using the method developed by Gall and Gall (1980). Seventeen days after immunization the rabbits were challenged by injecting 0.5 ml of sterile BSA (30%) in saline into the right knee joint. An equal amount of saline was injected into the left knee to serve as the control. Synovial fluid was collected daily up to 28 days for total and differential leucocyte counts (TLC and DLC).

Sodium urate-induced gouty arthritis in dogs

The knee joint of mongrel dogs of either sex (6–9 kg) organized into groups of four were injected with 0.5 ml of sterilized normal saline containing 10 mg sodium urate crystals 1 h after oral drug treatment (Faires et al., 1962). The animals were observed for inflammation of the joint, total leucocyte count and typical three legged gait.

Carrageenan-induced pleurisy in rats

Pleurisy was induced by injecting 0.5 ml of carrageenan (1% w/v) into the pleural cavity of rats organized into groups of 5 (Meacock and Kitchen, 1979).

Effect on serum transaminases in arthritic rats

Established arthritis was produced as described above. BA was orally administered for 2 weeks and at the termina-

tion of study, blood was collected for estimation of serum transaminases (Hanson, 1963).

Effect on gestation, litter size and post-partum bleeding in rats

Female rats organized into groups of 5 were used as described by Aiken (1972) on days 18 to 21 of gestation. The drug was orally administered twice daily. Animals were observed during the gestation period.

Effect on castor oil-induced diarrhea in rats

Rats that were fasted overnight were organized into groups of five and were administered the drug orally. After 1 h, castor oil (1 ml/100 g p.o.) was administered and the animals observed for the onset and character of diarrhea (Awouters et al., 1978).

Ulcerogenic effect in rats

Using Cashin's method (1977), the test drug was administered to rats fasted overnight. The animals were sacrificed 3 h after dosing, their stomachs removed, cut along the lesser curvature and scored according to the arbitrary scale.

Analgesic activity in mice

Analgesic activity was determined in mice organised into groups of 10 using the tail clip method of Bianchi and David (1960) and the acetic acid-induced writhing syndrome (Witkin et al., 1961).

Antipyretic activity in rats and rabbits

Pyrexia was produced in rats by injecting 2 ml of yeast (15% w/v) suspension in gum acacia (2% w/v) (Brownlee, 1937) and in rabbits (n=4) by *i.v.* injecting 0.1 ml of TAB vaccine. Test compounds were administered when pyrexia was maximal. Hourly temperature, were recorded up to 4 h.

Results and discussion

The findings of this study shows BA to possess varying degrees of AIA in dose-related patterns in a variety of acute and chronic test models. In acute tests, BA in a dose range of 50–200 mg/kg administered orally elicited AIA of 26–43% in rats, of 20–34% in mice with carrageenan induced edema, of 21–51% in dextran-induced edema in rats and 18–37% in histamine-induced edema in rats (Fig. 1). The AIA of BA was not affected in adrenalectomised rats, thereby ruling out the possibility of its activation by the pituitary adrenal axis (Fig. 1). This was further supported by

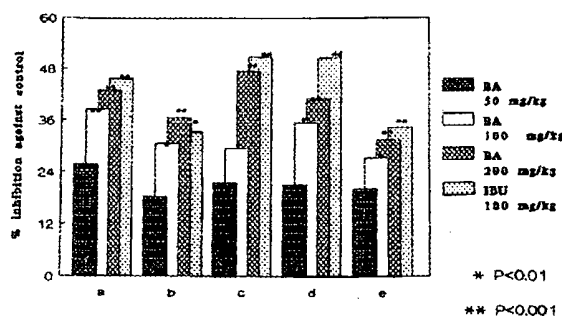


Fig. 1. Anti-inflammatory effect of BA orally administered on edema induced by carrageenan (a), histamine (b), dextran (c), carrageenan in adrenalectomised rats (d) and carrageenan in mice (e). Each value denotes the mean of 5 animals. Level of significance determined by using student's T-test.

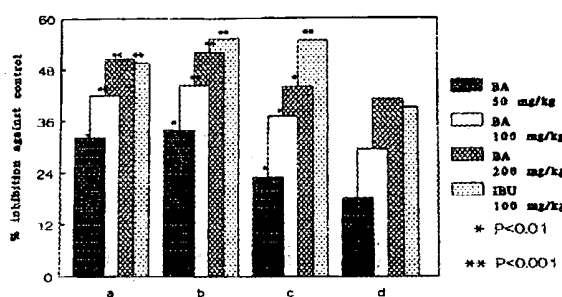


Fig. 2. Dose-related anti-arthritic activity of BA upon oral treatment for: developing adjuvant arthritis (a) and established adjuvant arthritis (b) in rats following injection of 0.05 ml of *Mycobacterium tuberculosis* (0.5% w/v) into the left hind foot; [formaldehyde arthritis (2% v/v formaldehyde) into the hind paw on 1st and 3rd day of experiment (c)] and gouty arthritis (d) induced by injecting 10 mg sodium urate crystals contained in 0.5 ml of sterile normal saline into the left stifle joint of dogs.

Each value represents the mean of 5 rats and 4 dogs. Level of significance determined by using student's T-test.

its weak inhibitory action in cotton pellet-induced granuloma in rats, which is considered to be more sensitive to steroidal type drugs and where NSAIDs show poor activity (DiRosa et al., 1979). Enhanced vascular permeability is a characteristic event in acute inflammation; BA (50–200 mg/kg p.o.) inhibited vascular permeability by 32 to 44%.

In chronic tests using the developing adjuvant polyarthritis, BA in doses of 50–200 mg/kg produced marked anti-arthritic activity of 32 to 50% (Fig. 2). BA also significantly reduced the development of secondary lesions. In similar doses it exerted marked inhibitory action (34–52%) in established adjuvant arthritis in rats, suggesting its possible usefulness as a therapeutic agent. Its reversal of syndromes of established arthritis indicates that it can control the damage caused by immunological mechanisms. The

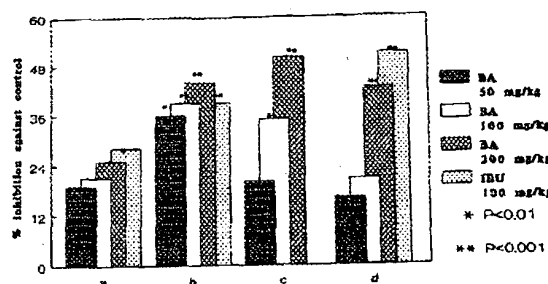


Fig. 3. Inhibitory action of orally administered BA on pleural exudate volume (a), total leucocyte counts (b) in carrageenan induced pleurisy in rats following 0.5 ml injection of carrageenan (1% w/v) into the pleural cavity, total leucocyte counts in BSA induced arthritis in rabbits (c). The animals were challenged with 0.5 ml of 30% BSA in sterile saline into the right knee 17 days after immunization. Synovial fluid was collected on different days with the final collection being made on day 28, and on TLC determined from the aspirated synovial fluid from the stifle joint of gouty arthritis dogs (d).

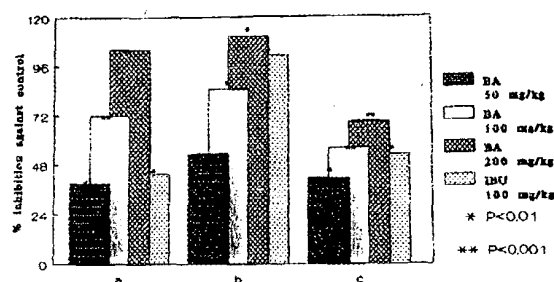


Fig. 4. Inhibitory effect of BA orally administered on arthritis elevated levels of serum glutamic oxaloacetic transaminase (SGOT) (a), serum glutamic pyruvic transaminase (SGPT) (b) and alkaline phosphatase (c).

Each bar represents the mean of 5 rats. Significance different from control determined using the student's T-test.

AIA of BA was further substantiated by their inhibitory action on serum glutamic oxaloacetic transaminase (SGOT), serum glutamic pyruvic transaminase (SGPT) and alkaline phosphatase levels enhanced by chronic inflammation in established adjuvant arthritis in rats (Fig. 4). In formaldehyde arthritis in rats, BA (50–200 mg/kg p.o.) displayed AIA in 23–44% of the cases (Fig. 2). Since migration of leucocytes plays an important role in the development of inflammatory conditions, inhibition of their migration might account for part of a drug's anti-inflammatory action. In our study on BSA-induced arthritis in rabbits, treatment with BA in multiple oral doses (25–100 mg/kg) reduced the leucocyte count of in the aspirated synovial fluid (Fig. 3). Single intrapatellar injections of BA (5–20 mg/knee) elicited a similar effect. Similarly administration of BA (50–200 mg/kg p.o.) in sodium urate gouty arthritis in

dogs, reduced leucocyte counts in synovial fluid by 16 to 42% (Fig. 3) and lessened the swelling of the stifle joint (Fig. 2). Dogs treated with BA showed moderate to marked improvement in their gait, whereas untreated dogs displayed a typical three-legged walk and evinced pain when made to move.

In the carrageenan-induced pleurisy test in rats, BA markedly reduced exudate volume (19–25%) and TLC by 36–44% (Fig. 3). These inhibitory results of BA on leucocyte migration may be attributed to the inhibition of release or formation of chemotactic factors (Sell, 1980). BA at 100 and 200 mg/kg p.o. lowered pyrexia in rats and rabbits by 1 to 2 °C. BA failed to exhibit any ulcerogenic effect in doses as high as 1000 mg/kg in rats. On the other hand, 200–500 mg/kg of BA administered orally exhibited a protective effect on HCL-alcohol and indomethacin-induced ulcers in rats (unpublished data).

A strong correlation has been reported between the potency of NSAIDs as inhibitors of PGs synthesis and as irritants of the gastrointestinal tract (Boyle et al., 1982; Cashin et al., 1977). BA lacked any ulcerogenic action. Inhibition of PG synthetase is a common mode of inhibitory action in NSAIDs (Vane, 1971). Like other NSAIDs, BA possess prominent anti-inflammatory but weak anti-pyretic activities. The absence of analgesic activity and especially the lack of ulcerogenic effects in the stomachs of tested rats suggests that BA do not act primarily by inhibiting PG synthesis. This is further supported by the fact that unlike other NSAIDs orally administered BA (50–200 mg/kg) failed to prolong the gestation period and parturition time in pregnant rats and did not affect the onset time of castor oil-induced diarrhea in rats – effects that have been attributed to the inhibition of PG synthesis (Aiken, 1972; 1974; Awouters et al., 1978). Using an *in vitro* test system of endogenous arachidonic acid in rat peritoneal neutrophils, Safayhi et al. (1992) reported that BA has a strong inhibitory action on the formation of the 5-lipoxygenase product, leukotriene LTB_4 , in a concentration-related manner, thereby supporting our findings. In a pilot clinical trial 60 patients with rheumatoid arthritis demonstrated significant improvement regarding morning stiffness, pain, swelling of various joints, and restored functional activity following 6–8 weeks treatment with BA (Singh et al., 1987).

In conclusion, BA are a new class of NSAID based on a natural source that has a novel mode of inhibitory action on the formation of 5-lipoxygenase product leukotriene (LTB_4). Lacking the ulcerogenic effect of other classical anti-inflammatory drugs, they emerge as unique candidates to be a drug with immense therapeutic value for the treatment of rheumatoid arthritis.

Acknowledgement

The authors are thankful to Shri G.L. Dhar for typing the manuscript.

References

- Aiken, J. W.: Aspirin and indomethacin prolong parturition in rats: Evidence that prostaglandins contribute to expulsion of Fetus. *Nature (Lond.)* 240: 21-25, 1972.
- Aiken, J. W.: Prostaglandins and prostaglandin inhibitors: studies on uterine motility and function. In: Robinson, H. J. and Vane, J. R. (Eds) prostaglandin synthetase inhibitor, 289-301, 1974. New York, Raven Press.
- Ammon, H. P. T., Mack, T., Singh, G. B. and Safayhi, H.: Inhibition of leukotriene B₄ formation in rat peritoneal neutrophils by an ethanolic extract of gum resin exudate of *Boswellia serrata*. *Planta Med.* 57: 203-207, 1991.
- Awouters, F., Niemegeers, C. J. E., Lenaerts, F. M. and Janseen, P. A. J.: Delay of castor oil diarrhea in rats: a new way to evaluate inhibitors of prostaglandin biosynthesis. *J. Pharm. Pharmacol.* 30: 41-45, 1978.
- Bianchi, C. and David, A.: Analgesic properties of 4-ethoxycarbonyl-1-(2-hydroxy-3-phenoxypropyl)-4-phenyl piperidine (B.D.H. 200) and some related compounds. *J. Pharm. Pharmacol.* 12: 449-459, 1960.
- Boyle, E. A., Freeman, P. C., Mangan, F. R., Thomson, M. J.: Nabumetone (BRL 14777, 4-[6-methoxy-2-naphthyl]-butan-2-one): a new antiinflammatory agent. *J. Pharm. Pharmacol.* 34: 562-569, 1982.
- Brownlee, G.: A comparison on the anti-pyretic activity and toxicity of phanactin and aspirin. *J. Pharm. Pharmacol.* 10: 609-620, 1937.
- Cashin, C. H., Dawson, W. and Kitchen, E. A.: The Pharmacology of benoxaprofen (2-(4-chlorophenyl-methyl-5-benzoxazole acetic acid), LRC I 3794, a new compound with anti-inflammatory activity apparently unrelated to inhibition of prostaglandin synthesis. *J. Pharm. Pharmacol.* 29: 330-336, 1977.
- DiRosa, M.: Inhibition of cell migration *in vivo* and granuloma formation. In: Vane, J. R. and Ferreira, S. H. (Eds): Hand book of experimental pharmacology, 59/II Springer Verlag, Berlin, Heidelberg, New York, 223-254, 1979.
- Gall, E. P. and Gall, E. A.: Histopathogenesis of bovine serum albumin induced arthritis in the rabbit. *J. Rheumatol.* 7: 13-23, 1980.
- Hanson, A. P.: Quoted in Methods of enzymatic analysis. 842, 1959, (ed): Bergmeyer, H. U. (1963) Lond. Academic press.
- Horakova, Z. and Muratova, J.: Means of influencing the oedematous component of inflammation. In: International Symposium on nonsteroidal anti-inflammatory drugs, 237-244, 1964.
- Faires, J. S. and McCarty, D. J. Jr.: Acute arthritis in man and dog after intrasynovial injection of sodium urate crystals. *Lancet* 2: 682, 1962.
- Meacock, S. C. R. and Kitchen, E. A.: Effects of the non-steroidal anti-inflammatory drug benoxaprofen on leucocyte migration. *J. Pharm. Pharmacol.* 31: 366-370, 1979.
- Newbould, B. B.: Chemotherapy of arthritis induced in rats by mycobacterial adjuvant. *Br. J. Pharmacol.* 21: 127-136, 1963.
- Newbould, B. B.: The pharmacology of Fenclozic acid 2-(4-chlorophenyl)thiazol-4-ylactic acid: I. C.I. 54, 450; Myales: a new compound with anti-inflammatory, analgesic and anti-pyretic activity. *Br. J. Pharmacol.* 35: 487-497, 1969.
- Safayhi, H., Mack, T., Sabieraj, J., Anazodo, M. I., Subramanian, L. R. and Ammon, H. P. T.: Boswellic acids: Novel, specific, Nonredox inhibitor of 5-lipoxygenase. *J. Pharm. Exp. Ther.* 261: 1143-1146, 1992.
- Sell, S.: Arthus (Toxic complex) reaction. In: Immunology, immunopathology and immunity, 3rd Edn. 242-283, 1980. Harper and Row Hagerstown, M.D.
- Selye, H.: Further studies concerning the participation of adrenal cortex in the pathogenesis of arthritis. *Brit. M. J.* 2: 1129-1135, 1949.
- Singh, G. B., Kour, Sukhvir, Satti, N. K., Atal, C. K. and Maheshwari, J. K.: Anti-inflammatory activity of *Euphorbia acaulis* Roxb. *J. Ethnopharmacol.* 10: 225-233, 1984.
- Singh, G. B. and Atal, C. K.: Pharmacology of an extract of salai-guggal ex-*Boswellia serrata*, a new non-steroidal anti-inflammatory agent. *Agents and Actions* 18: 407-412, 1986.
- Singh, Hardayal, Singh, G. P., Walia, R., Sidhu, P., Manesh, H. S., Bajaj, V. K. and Singh, G. B.: Open and doubleblind studies on antiarthritic activities of boswellic acids (B. A.) Abstract presented at International Conference on clinical pharmacology and therapeutics held at Bombay (India), 20-22 Nov, FPS 8/5, 1987.
- Singh, G. B., Singh, Surjeet, Bani, S., Gupta, B. D. and Banerjee, S. K.: Anti-inflammatory activity of oleanolic acid in rats and mice. *J. Pharm. Pharmacol.* 44: 456-458, 1992.
- Singh, G. B., Bani, Sarang, Singh, Surjeet, Khajuria, A., Sharma, M. L., Gupta, B. D. and Banerjee, S. K.: Anti-inflammatory activity of the irridoids kutkin, Picroside-1 and Kutkoside from *Picrothiza kurroa*. *Phytotherapy Research* 7: 402-407, 1993.
- Singh, G. B., Singh, Surjeet and Bani, Sarang: Boswellic acids - anti-inflammatory, anti-arthritis and anti-pyretic. *Drugs of Future* 18: 307-309, 1993.
- Singh, G. B. and Singh, Surjeet: Antiinflammatory activity of *Lanena coromandelica* bark extract in rats. *Phytotherapy Research* 8: 311-313, 1994.
- Singh, Surjeet, Bani, S., Khajuria, A., Sharma, M. L., Singh, G. B., Suri, A. K. and Srivastava, T. N.: Antiinflammatory activity of *Paederia foetida*. *Fitoterapia LXV*: 357-365, 1994.
- Vane, J. R.: Inhibition of prostaglandin synthesis as a mechanism of action of aspirin like drugs. *Nature (New Biol.)* 231: 232-235, 1971.
- Whittle, B. A.: The use of changes in capillary permeability in mice to distinguish between narcotic and non-narcotic analgesics. *Br. J. Pharmacol.* 22: 246-253, 1964.
- Winter, C. A.: Anti-inflammatory testing methods: Comparative evaluation of indomethacin and other agents. In: international Symposium on nonsteroidal anti-inflammatory Drugs. (eds): Garattini, S. and Dukes, M. N. G. Excerpta Medica Foundation, Amsterdam. 190-202, 1964.
- Winter, C. A. and Porter, C. C.: Effects of alterations in side chain upon anti-inflammatory and liver glycogen activities of hydrocortisone esters. *J. Am. Pharm. Assoc. Sc. Ed.* 46: 515-519, 1957.
- Winter, C. A., Risley, E. A. and Nuss, G. W.: Carrageenan-induced oedema in hind paw of rat as an assay for anti-inflammatory drugs. *Proc. Soc. Biol. Med.* 111: 544-547, 1962.
- Witkin, L. B., Heubner, C. E., Galdi, F., O'Keefe, Spilatetta, P. and Plummer, A. J.: Pharmacology of 2-amino-indane hydrochloride (Su-8629): a potent non-narcotic analgesic. *J. Pharm. Exp. Ther.* 133: 400-408, 1961.

Address

G. B. Singh, Department of Pharmacology, Regional Research Laboratory, Canal Road, Jammu-Tawi 180 001, India.

STIC-ILL

From: Jiang, Shaojia
Sent: Monday, November 01, 2004 6:11 PM
To: STIC-ILL
Cc: Jiang, Shaojia
Subject: please pull out these 09/926424

NPL ☒ Adonis _____
MIC _____ BioTech _____ MAIN _____
NO _____ Vol NO _____ NOS _____
Ck Cite _____ Dupl Request _____
Call # _____

9 ANSWER 38 OF 50 CAPLUS COPYRIGHT 2004 ACS on STN DUPLICATE 7

ACCESSION NUMBER: 1996:491734 CAPLUS
DOCUMENT NUMBER: 125:185262
TITLE: Anti-inflammatory actions of boswellic acids
AUTHOR(S): Singh, G. B.; Singh, Surjeet; Bani, Sarang
CORPORATE SOURCE: Regional Research Laboratory, Department
Pharmacology,
Jammu Tawi, 180 001, India
SOURCE: Phytomedicine (1996), 3(1), 81-85
CODEN: PYTOEY; ISSN: 0944-7113
PUBLISHER: Fischer
DOCUMENT TYPE: Journal
LANGUAGE: English

ACCESSION NUMBER: 1999206199 EMBASE
TITLE: [Salai Guggal - Indian incense for therapy of rheumatoid
arthritis].
SALAI GUGGAL - INDISCHER WEIHRAUCH ZUR BEHANDLUNG DER
RHEUMATOIDEN ARTHRITIS.
AUTHOR: Trubestein G.
CORPORATE SOURCE: Dr. G. Trubestein, An der Heppenmauer 10, D-63619 Bad
Orb,
Germany
SOURCE: Biologische Medizin, (1999) 28/3 (121-124).
Refs: 21
ISSN: 0340-8671 CODEN: BIMEFA
COUNTRY: Germany
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 029 Clinical Biochemistry
031 Arthritis and Rheumatism
037 Drug Literature Index
LANGUAGE: German
SUMMARY LANGUAGE: English; German

ACCESSION NUMBER: 2001:447633 CAPLUS
DOCUMENT NUMBER: 135:220902
TITLE: Anti-tumor and anti-carcinogenic activities of
triterpenoid, .beta.-boswellic acid
AUTHOR(S): Huang, Mou-Tuan; Badmaev, Vladimir; Ding,
Yu; Liu, Yue; Xie, Jian-Guo; Ho, Chi-Tang
CORPORATE SOURCE: Laboratory for Cancer Research, College of Pharmacy,
Rutgers University, Piscataway, NJ, 08854-8020, USA
SOURCE: BioFactors (2000), 13(1-4), 225-230
CODEN: BIFAEU; ISSN: 0951-6433
PUBLISHER: IOS Press

Original report

Anti-tumor and anti-carcinogenic activities of triterpenoid, β -boswellic acid

Mou-Tuan Huang^{a,*}, Vladimir Badmaev^b, Yu Ding^a, Yue Liu^a, Jian-Guo Xie^a and Chi-Tang Ho^c

^aLaboratory for Cancer Research, College of Pharmacy, Rutgers University, Piscataway, NJ 08854-8020, USA

^bSabinsa Corp, Piscataway, NJ 08854, USA

^cDepartment of Food Science, Cook College, Rutgers University, Piscataway, NJ 08854-8020, USA

Abstract. Boswellin (BE), a methanol extract of the gum resin exudate of *Boswellia serrata*, contains naturally occurring triterpenoids, β -boswellic acid and its structural related derivatives, has been used as a traditional medicine for the treatment of inflammatory and arthritic diseases. Topical application of BE to the backs of mice markedly inhibited 12-*O*-tetradecanoylphorbol-13-acetate (TPA)-induced increases in skin inflammation, epidermal proliferation, the number of epidermal cell layers, and tumor promotion in 7,12-dimethylbenz[a]anthracene (DMBA)-initiated mice. Feeding 0.2% of BE in the diet to CF-1 mice for 10–24 weeks reduced the accumulation of parametrial fat pad weight under the abdomen, and inhibited azoxymethane (AOM)-induced formation of aberrant crypt foci (ACF) by 46%. Addition of pure β -boswellic acid, 3-*O*-acetyl- β -boswellic acid, 11-keto- β -boswellic acid or 3-*O*-acetyl-11-keto- β -boswellic acid (Fig. 1) to human leukemia HL-60 cell culture inhibited DNA synthesis in HL-60 cells in a dose-dependent manner with IC₅₀ values ranging from 0.6 to 7.1 μ M. These results indicate that β -boswellic acid and its derivatives (the major constituents of Boswellin) have anti-carcinogenic, anti-tumor, and anti-hyperlipidemic activities.

Keywords: Boswellin, triterpenoid, triterpene acid, boswellic acid, cancer prevention

1. Introduction

The plant *Boswellia serrata* grows widely in India. The gum resin exudate of *B. serrata* is collected from the stem of the plant *B. serrata* and is used as a commercial source for the herbal medicine [1]. Boswellin (BE) is an extract of the gum resin of *B. serrata* (a trade name of Sabinsa Corp., NJ). The anti-inflammatory activity and anti-arthritis pain of β -boswellic acids (the major constituents of BE) is due to their ability to inhibit 5-lipoxygenase activity [1–4]. Rats when treated orally with BE and β -boswellic acids in the range of 50–200 mg/kg of body weight showed anti-arthritis activity comparable to phenylbutazone [5]. Treatment of humans or horses with BE or β -boswellic acids resulted in improvement of arthritic conditions [1,5,6]. The gum resin exudate of *B. serrata* also has anti-hyperlipidemic and

*Correspondence to: Dr. Mou-Tuan Huang, Laboratory for Cancer Research, College of Pharmacy, Rutgers, The State University of New Jersey, Piscataway, NJ 08854-8020, USA. Tel.: +1 732 445 3400 ext 252; Fax: +1 732 445 0687; E-mail: mthuang@rci.rutgers.edu.

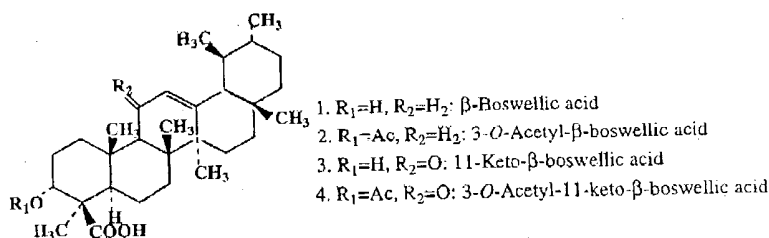


Fig. 1. Chemical structures of β -boswellic acid and its derivatives.

anti-atherosclerotic activities [7,8]. We now report that topical application of BE inhibited TPA-induced skin inflammation, epidermal proliferation and skin tumor promotion. We also show that BE has anti-hyperlipidemic activity and inhibits AOM-induced formation of ACF (early colon tumor marker) as well as anti-tumor activity of pure boswellic acid and its derivatives.

2. Materials and methods

2.1. Preparation of Boswellin and chemical composition

Oleogum resin exudate of *B. serrata* (100 g) was extracted with methanol ($200\text{ ml} \times 3$), the methanol evaporated in vacuum to give 45 g of dried extract. The dried extract (30 g) was dissolved in 2% KOH solution (200 ml). The ethyl acetate extract was discarded, and the aqueous solution was neutralized with 2% HCl to pH 6.0, and then extracted with ethyl acetate ($5 \times 150\text{ ml}$). The combined ethyl acetate solution was washed with water, and dried with anhydrous Na_2SO_4 overnight, and then evaporated to dryness to produce 18 g of residue (Boswellin, a mixture of boswellic acid and its derivatives). Boswellin contains about 13–18% β -boswellic acid, 11–17% 3-O-acetyl- β -boswellic acid, 6–8% 11-keto- β -boswellic acid, and 4–7% 3-O-acetyl-11-keto- β -boswellic acid.

2.2. Preparation of pure β -boswellic acid, 3-O-acetyl- β -boswellic acid, 11-keto- β -boswellic acid, 3-O-acetyl-11-keto- β -Boswellic acid.

Further separation and purification of Boswellin to pure boswellic acid and its derivatives as described in our previous publication [9].

2.3. Animals

CD-1 female mice (23–25 days for ear edema experiments, or 6–7 weeks old for skin tumor experiment) were purchased from Charles River Laboratories (Kingston, NY). The mice were kept in our animal facility for at least 1 week before use. Mice were fed with a Purina Laboratory Chow 5001 diet from Ralston-Purina Co. (St. Louis, MO) and water ad libitum and kept on a 12 h light/12 h dark cycle. The dorsal region of each mouse was shaved with electric clippers at least 2 days before treatment with TPA or DMBA. Only mice that did not show signs of hair regrowth were used.

2.4. Quantification of aberrant crypt foci

Female CF-1 mice (5–6 weeks old; 10–30 mice per group) were received s.c. injection of AOM (5, 10, 10, 10 mg/kg) once a week (total 4 injections). The test compounds in the diet are given to mice at 2 weeks before the first AOM injection, during, and continuing until the end of the experiment (initiation + post-initiation period). At 24 weeks after the last dose of AOM injection, the mice were killed and colon (from anus to caecum) was removed, opened longitudinally, rinsed with normal saline solution, and stapled on a plastic sheet. The colon samples were placed in a 10% neutral buffered formalin solution for 24 hours. The entire colon was stained with 0.2% methylene blue dissolved in phosphate buffer saline (PBS) solution for 20 minutes. The whole mount of colon samples were examined in a light microscope. Only ACF meeting the criteria with crypts of increased size with a thicker and deeply stained epithelial lining and an increased pericryptal zone compared with normal crypts were chosen.

2.5. Determination of proliferation of epidermis by bromodeoxyuridine (BrdUr) labeling index

Immunohistochemical staining for BrdUr was performed according to the procedure of the commercial assay kit as described in our previous publication [10].

2.6. Measurement of edema of mouse ears

Measurement of mouse ear edema was done according to the following procedure. Both ears of female CD-1 mice (23–25 days old; 5–6 mice per group) were treated topically with 20 μ l acetone, 0.5 nmol TPA in acetone or Boswellin together with 0.5 nmol TPA in acetone. Five hours later the mice were sacrificed by cervical dislocation, and 6-mm (diameter) ear punches biopsies were taken and weighed. The increases in weight of the ear punches were directly proportional to the degree of inflammation.

2.7. Tumor studies on mouse skin

The dorsal region of CD-1 female mice (8 weeks old) were shaved with electric clippers. For studies on the inhibitory effect of topical application of Boswellin on TPA-induced tumor promotion, the mice (30 per group) were treated topically with 200 nmol of 7,12-dimethylbenz[a]anthracene (DMBA) in 100 μ l of acetone. A control group of mice received 200 μ l of acetone alone. After 1 week the mice were treated topically with 200 μ l of acetone, 5 nmol of TPA, or 5 nmol of TPA together with 1.2 or 3.6 mg of Boswellin (BE) in acetone twice weekly for 18 weeks. Skin tumors greater than 1 mm in diameter were counted and recorded every 2 weeks. All skin tumors were examined histopathologically.

3. Results

3.1. Inhibitory effect of topical application of BE on TPA-induced biomarker changes

The possibility that BE could inhibit TPA-dependent inflammation was evaluated by studying the effects of BE on TPA-induced edema of mouse ears. Topical application of 0.06–0.24 mg of BE with 0.5 nmol to the ears of mice inhibited TPA-induced edema by 40–84% (Table 1). BE strongly inhibited TPA-induced proliferation of mouse epidermis as determined by the incorporation of bromodeoxyuridine (BrdUr) into epidermal DNA. Twenty four hours after the last dose of topical application of 5 nmol of TPA once a day for 2 days resulted in a 43% BrdUr labeling index. Topical application of 3.6 mg of BE together with 5 nmol of TPA once a day for 2 days results in a decrease BrdUr labeling index to 8.3%. Thus BE inhibited TPA-induced epidermal proliferation by 81% at 3.6 mg.

Table 1
Effect of boswellic acids and Boswellin extract on TPA-induced edema of mouse ears

Treatment	Weight per ear punches (mg/punch)	Percent inhibition (%)
Acetone	6.4 \pm 0.16	—
TPA	13.9 \pm 0.45	—
TPA + Boswellin Ext (0.06 mg)	10.9 \pm 0.84	40
TPA + Boswellin Ext (0.12 mg)	8.4 \pm 0.56	75
TPA + Boswellin Ext (0.24 mg)	7.6 \pm 0.10	84

Female CD-1 mice (23–25 days; 5 mice for group 2, 4 mice for all other group) were treated topically 20 μ l acetone, 0.5 nmol TPA or TPA and various doses of boswellin extract (BE) in 20 μ l acetone. Five hours later, the mice were killed and ear punches were weighed. Data are represented as means \pm SE.

3.2. Inhibitory effect of topical application of BE on TPA-induced tumor promotion in the epidermis of mice previously initiated with DMBA

BE strongly inhibited TPA-induced skin tumor promotion in the epidermis of female CD-1 mice previously treated with DMBA. Female CD-1 mice initiated with a single dose of 200 nmol DMBA and promoted with 5 nmol of TPA twice weekly for 16 weeks developed an average of 15.8 skin tumors per mouse and 90% of the mice had skin tumors. Topical application of 5 nmol TPA together with 1.2 or 3.6 mg of BE for 16 weeks reduced the number of skin tumors per mouse by 87 and 99%, respectively. The percentage of mice with skin tumor was decreased by 59 or 92%, when topically applied with 1.2 or 3.6 mg of BE together with 5 nmol of TPA twice weekly for 16 weeks. BE treatment delayed the appearance of the first skin tumor. The latent time for 1.2 mg of BE treatment was 4 weeks and was greater than 8 weeks with 3.6 mg of BE treatment. These results suggest that BE is a potent inhibitor of TPA-induced skin tumor promotion on mouse skin.

3.3. Effect of oral administration of BE in the diet on the accumulation of parametrial fat pad under abdomen

Oral administration of 0.2% BE in the diet to female CF-1 mice for 11 weeks reduced the accumulation of parametrial fat pad under abdomen in CF-1 mice. Feeding with Western style diet to female CF-1 mice for 11 weeks induced the weight accumulation of the parametrial fat pad to 1.64 g. Feeding 0.2% BE in Western diet for 11 weeks resulted parametrial fat pad 0.91 g. The result indicates feeding BE diet decreased accumulation of parametrial fat pad by 46%.

3.4. Effect of dietary BE on azoxymethane (AOM)-induced formation of aberrant crypt foci in colon epithelium

Female CF-1 mice received AOM (5, 10, 10, 10 mg AOM/Kg body weight) at 6 weeks of age once every 4 days and AOM (10 mg/kg body weight) once at 24 weeks. The mice were killed at 35 weeks after the first dose of AOM. The mice received AIN 76A diet or 0.2% BE in AIN 76A diet at 2 weeks before the first dose of AOM, and continued until the end of the experiment. In the control diet group, the average number of aberrant crypt foci per colon was 5.2, and the average of number aberrant crypts per colon was 37. The average number of ACF per colon in mice fed with 0.2% BE in the diet was 3.1 (inhibition of 40%). The average of AC per colon in fed with 0.2% BE in the diet was 6.8 AC per colon

Table 2
Effect of dietary bowellin (BE) on azoxymethane (AOM)-induced formation of aberrant crypt foci (ACF) in CF-1 mice

	Positive control	0.2% BE	0.5% BE
ACF/colon	5.2 \pm 1.2	3.1 \pm 1.4 (40%)	3.3 \pm 1.4 (37%)
AC/colon	37 \pm 5.9	6.8 \pm 1.1 (82%)	8.8 \pm 2.5 (76%)

Female CF-1 mice received AOM (5, 10, 10, 10 mg AOM/Kg) at 6 weeks of age once every 4 days and AOM (10 mg/Kg) once at 24 weeks after the first dose of AOM. The mice received AIN 76A diet or test compound in AIN 76A diet at 2 weeks before the first dose of AOM, and continuing until the end of the experiment. The data are expressed as the mean \pm SE. Data in parentheses are % inhibition.

Table 3
The effect of β -boswellic acid and its derivatives on the synthesis of DNA in human leukemia HL-60 cells

Compound	IC ₅₀ (μ M)
1. β -Boswellic acid	3.7
2. 3-O-Acetyl- β -boswellic acid	1.4
3. 11-Keto- β -boswellic acid	0.9
4. 3-O-Acetyl-11-keto- β -boswellic acid	0.6

(82% inhibition see Table 2). The results indicated that dietary BE strongly inhibited AOM-induced formation of the number of ACF per colon and AOM-induced progression from early stage to late stage of ACF.

3.5. Inhibitory effect of pure β -boswellic acid and its pure derivatives on the synthesis of DNA in HL-60 cells

All 4 pure triterpene acids, β -boswellic acid, 3-O-acetyl- β -boswellic acid, 11-keto- β -boswellic acid, and 3-O-acetyl-11-keto- β -boswellic acid inhibited DNA synthesis on human leukemia HL-60 cells in a dose-dependent manner with IC₅₀ values ranging from 0.6 to 7.1 μ M, among them compound 4,3-O-acetyl-11-keto- β -boswellic acid induced the most pronounced inhibitory effects on DNA synthesis with IC₅₀ value of 0.9 μ M (Table 3).

4. Discussion

The results of the present study demonstrate that topical application of BE inhibits TPA-induced mouse ear edema, TPA-induced epidermal proliferation, TPA-induced increases in the number of epidermal cell layers, and TPA-induced skin tumor promotion in CD-1 mice. Since β -boswellic acid is able to inhibit 5-lipoxygenase activity [2-4]. The anti-inflammatory, anti-tumor promoting and anti-arthritis activities may be due to its capability of inhibiting lipoxygenase activity [4-6]. All 4 pure β -boswellic acids inhibit DNA synthesis in human leukemia HL-60 cells in a dose-dependent manner with IC₅₀ values ranging from 0.6 to 7.1 μ M, among them 3-O-acetyl-11-keto- β -boswellic acid induced the most pronounced inhibitory effects on DNA synthesis with IC₅₀ value of 0.6 μ M [9], perhaps due to induction of differentiation and apoptosis in HL-60 cells by boswellic acid acetate [11]. In addition, feeding BE in

the diet to CF-1 mice also inhibits the accumulation of parametrial fat pad weight under abdomen, and inhibits AOM-induced formation of AFC in mouse colon epithelium. BE, pure β -boswellic acid and its derivatives may be proved to be broad cancer chemopreventive agents as well as anti-hyperlipidemic agents.

References

- [1] M. Majeed, V. Badmaev, S. Gopinathan, R. Rajendran and T. Norton, *Boswellin, The Anti-Inflammatory Phytonutrient*, Nutriscience Publishers, Inc., Piscataway, NJ, 1996.
- [2] H.P.T. Ammon, T. Mack, G.B. Singh and H. Safayhi, Inhibition of leukotriene B₄ formation in rat peritoneal neutrophils by an ethanolic extract of the gum resin exudate of *Boswellia serrata*, *Plant Med.* **57** (1991), 203–2037.
- [3] H. Safayhi, Mack, T., Sabieraj, J., Anazodo, M.I., Subramanian, L.R. and Ammon, H.P.T., Boswellic acids: novel, specific, non-redox inhibitors of 5-lipoxygenase, *J. Pharmacol. and Exp. Therapy* **261** (1992), 1143–1146.
- [4] H.P.T. Ammon, T. Safayhi, T. Mark and J. Sabieraj, Mechanism of anti-inflammatory actions of curcumin and boswellic acids, *J. Ethnopharmacology* **38** (1993), 113–119.
- [5] V.N. Gupta, D.S. Yadav, M.P. Jain and C.K. Atal, Chemistry and Pharmacology of the gum resin of *B. Serrata*, *India Drugs* **24** (1987), 221–231.
- [6] B. McCrea, Ancient Indian medical herb proving itself a winner for modern-day equine athletes, *J. Am. Hol. Vet. Med. Assoc.* **12** (1993), 19.
- [7] C.K. Atal, O.P. Gupta and G.B. Singh, Salai guggal: a promising anti-arthritic and anti-hyperlipidemic agent, *Brit. J. Pharm.* **74** (1981), 115–116.
- [8] U. Zutshi, Mechanism of cholesterol-lowering effect of salai guggal, *Ind. J. Pharm.* **18** (1986), 182–183.
- [9] Y. Shao, C-T. Ho, C-K. Chin, V. Badmaev, W. Ma and M-T. Huang, Inhibitory activity of boswellic acids from *Boswellia serrata* against human leukemic HL-60 cells in culture, *Planta Med.* **64** (1998), 328–331.
- [10] Y-P. Lu, Y-R. Lou, P. Yen, D. Mitchell, M-T. Huang and A.H. Conney, *Cancer Res.* **59** (1999), 4591–4602.
- [11] Y. Jing, S. Nakajo, L. Xia, K. Nakaya, Q. Fang, S. Waxman and R. Han, Boswellic acid acetate induces differentiation and apoptosis in leukemia cell lines, *Leuk. Res.* **23** (1999), 43–50.